REMARKS

A. The Status of the Claims and the Amendments

Claims 132-137, 142-145, 152-159, 161-163, 167, and 175-177 have been previously canceled without prejudice, as claims drawn to non-elected species. Claims 185-250 have been withdrawn as claims drawn to non-elected species.

By the present amendment, claims 116 and 164 have been amended to claim the invention with greater particularity and specificity. The matter introduced in the amendments was disclosed in the specification, as originally filed, and in the original claims. No new matter has been introduced in the amendments. Accordingly, entry of the amendment is respectfully requested.

Upon entry of this amendment, claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-250 will be pending, of which claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-184 are currently under consideration.

B. Restriction Requirement

The Examiner has declared that claims 185-250 are directed to non-elected species and *sua sponte* has withdrawn claims 185-250 from consideration (item 1, page 2 of the Office Action). The Applicant respectfully disagrees with this action.

The Applicant points out that claims 185-225 are directed to the subject matter that is present in claims which are under consideration. Specifically, each of claims 185 and 210 is directed to a method which includes the use of the bioactive agents each of which is recited in claim 160. The same applies to all the claims depending on either claim 185 (i.e., claims 186-209) or on claim 210 (i.e., claims 211-225). It has not been declared by the Examiner that claim 160 is directed to a non-elected invention, and claim

160 has not been withdrawn from consideration. To the contrary, claim 160 is before the Examiner and is under consideration. Clearly, claims 185-225 do not contain any matter that was not elected, since these claim combine the elected matter (i.e., a sum of claims 185 and 160, or claims 210 and 160). Accordingly, it is submitted that the withdrawal of claims 185-225 from consideration is improper.

With regard to claims 226-250, they are directed to a combination of original claims 121, 123, 124, 126, and 128. Each of claims 121, 123, 124, 126, and 128 is currently under consideration, and none was withdrawn as directed to a non-elected invention. Therefore, claims 226-250 that combine the matter that was elected cannot logically be directed to a non-elected invention. The Applicant respectfully reminds the Examiner that claims 226-250 were added in response to the suggestion made by the Examiner's during the interview on August 2, 2005. A copy of the summary of the interview is attached as Exhibit 1. It is submitted that it would be improper for the Examiner to suggest that certain claims be added, and then object to them as to claims directed to a non-elected invention after the Applicant has followed the Examiner's suggestion.

In view of the foregoing, reconsideration and reinstatement of claims 185-250 are respectfully requested.

C. First Rejection Under 35 U.S.C. § 103(a)

Claims 116-131, 138-141, 146-151, 160, 164-166, 168-170, 173, 174. and 178-184 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al. in view of U.S. Patent No. 5,648,098 to Porter (item 2, page 3 of the Office Action). This rejection is respectfully traversed.

The three basic criteria that must be met to establish a *prima facie* case of obviousness have been provided and discussed in responses to previous Office Actions.

Applicant submits that the Examiner has not established a *prima facie* case of obviousness.

More specifically, claims 116 and 164 have been amended and each now recites a method for the delivery of a bioactive agent from the vasculature to a selected tissue in a patient including a step of "delivering said bioactive agent from the vasculature into said selected tissue" by "cavitating and/or rupturing said vesicles" (claim 116) or by 'activating" the same (claim 164). The method requires " applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz."

Siegel et al. fail to describe or suggest a method which includes all the limitations recited in claims 116 and 164. Specifically, Siegel et al. only teach a method of thrombolysis (e.g., col. 2, lines 3-7). In Siegel et al. a thrombolytic agent is present only in the vasculature of the patient, where the agent in combination with ultrasound dissolves a thrombus. The agent in Siegel et al. never leaves the vasculature of the patient and there is nothing in Siegel et al. teaching or suggesting drug delivery into a tissue. In addition, Siegel et al. only teach that preferably the frequency between 24 and 53 KHz be used (col. 2, lines 46-47), especially 25-39 KHz (col. 7, lines 59-60) and possibly up to 243 KHz (col. 7, lines 46 and 57). There is nothing in Siegel et al. disclosing or suggesting the use of a high frequency such as 750 kHz to 3 MHz.

To cure these deficiencies of Siegel et al., the Examiner proposes to combine the teachings of Siegel et al. and Porter. Indeed, Porter mentions a possibility of using the ultrasound equipment capable of generating the signal with the frequency up to several megahertz, which includes the range of frequencies recited in claims 116 and 164.

However, such combination of references does not satisfy the criteria required to establish a *prima facie* case of obviousness. The Examiner has not shown that there is there any suggestion or motivation to modify the Siegel et al. reference by importing the

teachings of Porter. The Examiner has based his conclusion of combinability of Siegel et al. and Porter on the fact that Porter shows a possibility of using frequencies in the range claimed in claims 116 and 164 (see, page 6, lines 5-8 of the Office Action). The Applicant respectfully disagrees.

Previously, the Applicant presented that under the authority of *In re Browner*, the prior art reference itself must suggest the desirability of modification, i.e., in this case, Siegel et al. must suggest such desirability. The Applicant further submitted there is no such suggestion in Siegel et al. The Examiner has declined to accept this argument and has repeated that "the rejection relies only on optimization the ultrasound waves of the frequency described in Siegel" (see page 4, lines 10-11 of the Office Action). The Applicant is convinced that the approach taken by the Examiner is erroneous under the circumstances of this case.

The only reason in favor of optimization provided by the Examiner is that such optimization is possible because "Siegel does not discourage one of ordinary skill in the art to employ the frequencies instantly claimed" and that "Porter shows that the state of the art that does not discourage the use of instantly claimed ultrasound frequencies" (see page 5, lines 4-5, and page 6, lines 4-5 of the Office Action). Even if the Examiner's conclusion were correct, under the authority of *In re Browner*, a positive suggestion of the desirability of modification is needed. Mere lack of discouragement is not enough to create motivation to modify.

It appears to the Applicant that the Examiner is exploring "obvious-to-try approach." While this approach may be useful under some circumstances, generally, a claim can be obvious only if the prior art points in the general direction of the invention, thereby arguably making it obvious to try, and those skilled in the art would believe that what was pointed to by the prior art would have a reasonable expectation of success. *In re O'Farrell*, USPQ2d 1673 (Fed. Cir. 1988). It is now established that "obvious-to-try"

does not establish a *prima facie* case of obviousness when "trying" means to vary a parameter until one possibly arrived at a successful result, where the prior art gave no direction as to which of many choices were likely to be successful. This is exactly the situation here.

Previously, the Applicant explained that Siegel et al. teach that as the frequency is increased from 25 to 29, to 53, to 66, to 85, to 105, and finally to 243 KHz, the results on clot dissolution worsen very substantially, all other factors being equal (i.e., the degree of dissolution falls, respectively, from 99 %, to 86 %, to 45 %, to 44 % to 36 %, to 27 % and finally to 26 %) (see, col. 7, lines 55-57). Any further increase along this line of development is likely to make the results even worse and thus will not be productive of the improved results sought by the Applicants. Thus, it is clear that Siegel et al. provide no indication that moving towards higher frequencies may bring about any improvement. In fact, Siegel et al. teach precisely to the contrary. Accordingly, it is not obvious to try the frequencies recited in claims 116 and 164.

In addition, the Applicants respectfully disagree with the Examiner's statement that "Siegel does not discourage one of ordinary skill in the art to employ the frequencies instantly claimed." The evidence in the clearly leads to the opposite conclusion. It cannot be reasonably disputed that Siegel et al. explicitly teach that the results get worse when the frequency is increased from 25 KHz to 243, as described above. It is the Applicant's position that the results provided by Siegel et al. discourage those skilled in the art from moving towards even higher frequencies.

Certainly, optimization of frequencies that the Examiner relies upon is possible. However, the term "optimization" means "an act of improvement to achieve maximum efficiency." It is not optimization but a senseless loss of time to increase the frequency and to get results worse than before, and then increase the frequency again and to get

even worse results, and then increase the frequency yet again and to get even worse results still. It is submitted that no reasonably skilled artisan would follow such a path.

Therefore, it is submitted that one skilled in the art would not be motivated to modify the teachings of Siegel et al. towards the increase in frequency to 750 KHz or higher, because the teachings of Siegel et al. suggest that such modification will lead to worse results.

In addition, even if *arguendo* there were the motivation to combine Siegel et al. and Porter, a *prima facie* case of obviousness still cannot be made. It is elementary that a combination of references must directly teach or at least suggest every limitation of the claim at issue. Here, Siegel et al. teach a method as described above. Porter also teaches only thrombolytic agents and methods for use thereof. It is specifically emphasized in Porter that the invention is site specific (col. 2, lines 19-20), and accordingly applies only to the process of lysis within the patient's vasculature. No drug or another agent in Porter leaves vasculature and enters any tissue of the patient.

Accordingly, neither Siegel et al. nor Porter teach nor suggest any application other than thrombolysis. Clearly, even if the teachings of Siegel et al. and Porter are combined, the combination still fails to describe every limitation of claims 116 and 164.

In view of the foregoing it is submitted that each of claims 116 and 164 is patentably distinguishable over Siegel et al. in view of Porter. Each of claims 117-131, 138-141, 146-151 and 160 depends, directly or indirectly on claim 116 and is considered patentable for at least the same reason. Each of claims 165, 166, 168-174, and 178-184 depends, directly or indirectly on claim 164 and is considered patentable for at least the same reason. Reconsideration and withdrawal of the rejection of claims 116-131, 138-141, 146-151, 160, 164-166, 168-170, 173, 174. and 178-184 are respectfully requested.

D. Second Rejection Under 35 U.S.C. § 103(a)

Claims 116-120, 160, 164-166, 171-174, and 178-180 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,380,411 to Schlief in view of the article by Holmes et al. (Journal of Urology, vol. 144, pp. 159-163 (1990)) (item 6, page 6 of the Office Action). This rejection is respectfully traversed on the following grounds.

Shlief describes destroying tumor cells using microbubbles and ultrasound, but fails to teach that a biologically active agent is used or that the frequency of the ultrasound is between 750 kHz and 3 MHz, as required by claims 116 and 164. In addition, Shlief describes his methods only with respect to *in vitro* applications, but fails to teach *any in vivo* applications and thus does not describe the step of administering a composition to a patient. Also, since no *in vivo* applications are described, Shlief fails to teach a step of delivering the bioactive agent into a tissue, as required by claims 116 and 164 Holmes et al. fail to provide the description lacking in Shlief.

To make out a prima facie case of obviousness, the Examiner again relies on optimization and states that "the rejection is based on whether one of ordinary skill in the art can optimize a result-effective parameter that is described in prior art" (see page 6, lines 16-18 of the Office Action). The Applicant disagrees. As discussed in detail above, the ability to optimize is not the only factor; the prior art reference must also motivate one skilled in the art to make optimization and to suggest what path of optimization is desirable.

Holmes at al. teach use high energy shock waves for destroying prostate cancer tissues. Holmes et al. also utilizing chemotherapeutic agents in conjunction with the application of the shock waves. However, there is nothing in Holmes et al. teaching the use of ultrasound having between 750 kHz and 3 MHz. All that is disclosed that the

shock waves are generated by lithotripsy using a XL-1 experimental machine; and the operating frequency that was used was just one shock per second, which would correspond to the frequency of 1 Hz. The Examiner has not explained how the use of such low frequency would suggest using the frequencies that are recited. The frequency mentioned in Holmes et al. is well below the minimum level that is used in ultrasonic technologies (typically, 20 KHz, as well known to those skilled in the art). Thus, low frequency and high energy non-ultrasonic shock waves used in Holmes et al. provide no motivation to use the high frequencies recited in claims 116 and 164

It is clear that the successful treatment in Holmes is correlated to the number of shock waves, but there is nothing more that one skilled in the art can learn from Holmes et al. for the purposes of the present application. Accordingly, it is submitted that even if the teachings of Shlief and Holmes et al. are combined as suggested by the Examiner, the combination would still fail to disclose or suggest every limitation of claims 116 and 164.

In view of the foregoing it is submitted that each of claims 116 and 164 is patentably distinguishable over Shlief in view of Holmes et al. Each of claims 117-120, and 160 depends, directly or indirectly on claim 116 and is considered patentable for at least the same reason. Each of claims 165, 166, 171-174, and 178-180 depends, directly or indirectly on claim 164 and are considered patentable for at least the same reason. Reconsideration and withdrawal of the rejection of claims 116-120, 160, 164-166, 171-174, and 178-180 are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

No fee is believed to be due in connection with filing this paper. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A duplicate copy of this Transmittal sheet is enclosed.

Respectfully submitted,

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